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Original article

Synthesis of the tetracyclic core of chlorospermines

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ABSTRACT

Chlorospermines A and B are biologically interesting acridone natural products and recently isolated from *Glycosmis chlorosperma*. We report here a convergent approach to construct the tetracyclic core of the natural products. The two fragments are assembled together through Sonogashira coupling, and a *cis*-triene intermediate was prepared by using hydrosilylation/desilylation. A 6π-electrocyclization/aromatization sequence served as the key step of the synthesis, which formed the tetrasubstituted arene motif in one pot.

1. Introduction

Acridone alkaloids comprise a large family of biologically active natural products [1], some of which display significant anticancer activity [2]. Chlorospermines A and B (**1** and **2**, Fig. 1) are two polycyclic acridone alkaloids recently isolated by Litaudon and co-workers from the stem bark of *Glycosmis chlorosperma* [3]. The latter possesses remarkable inhibitory property against dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A), which is closely related to neuronal development and adult brain physiology. Although a number of acridone syntheses have been documented in literature [4–11], they usually relied on Friedel–Crafts reactions which require strongly acidic conditions as well as electron-rich arene substrates. In order to build up a focused library of chlorospermine analogs for further biological evaluations, an efficient and modular approach to the tetracyclic core of chlorospermines is highly desired. This approach needs to be applicable to a wide range of substrates; thus, constructing the acridone core under neutral conditions would be optimal.

The synthesis of multi-substituted arenes remains a remarkable challenge for modern organic chemistry [12–24]. Electrocyclization has proven to be a powerful tool for assembling functionalized ring systems, since Nicolaou *et al.* disclosed the elegant synthesis of endiandric acids [25–43]. Notably, multi-substituted arenes can be constructed in a highly efficient and convergent fashion, when 6π electrocyclization is strategically combined with oxidative aromatization [44–54]. Recently, we have successfully applied such strategies to the syntheses of a series of natural products containing aromatic moieties, such as daphenylline [55], tubingensin A [56], xiamycin A, oridamycins A and B [57], rubriflordilactone A [58] and clostrubin [59]. Herein, we report a concise route toward the tetracyclic core of chlorospermines A and B using 6π electrocyclization/aromatization as a key step.

2. Experimental

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) was distilled immediately before use from sodium-benzophenone ketyl. Methylene chloride (CH_2Cl_2) and triethylamine (Et_3N) were distilled from calcium hydride and stored under an argon atmosphere. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Solvents for chromatography were used as supplied by Titan chemical. Reactions were monitored by thin layer chromatography (TLC) carried out on S-2 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and aqueous ammonium cerium nitrate/ammonium molybdate or basic aqueous potassium permanganate as

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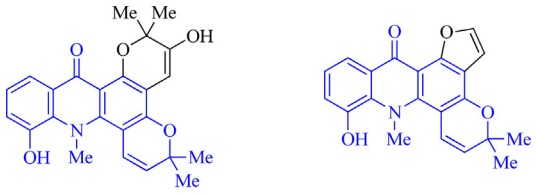


1: chlorospermine A **2**: chlorospermine B

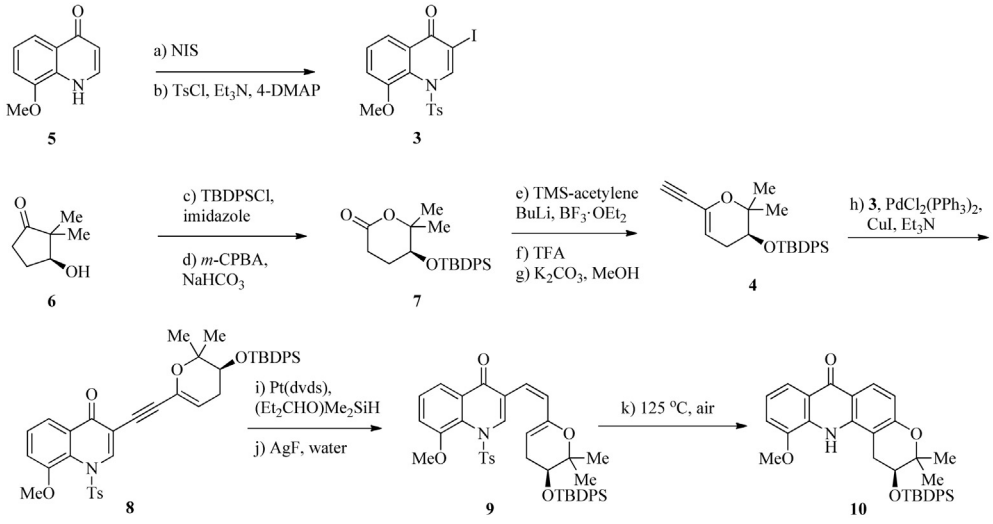
Fig. 1. The structures of chlorospermines A and B.

developing agent. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on Bruker AV-400 instrument and calibrated by using residual undeuterated chloroform (δ_H 7.26) and $CDCl_3$ (δ_C 77.16) as internal references. IR spectra were recorded on a Thermo Scientific Nicolet 380 FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on a Bruker APEXIII 7.0 Tesla ESI-FT.

The preparation of compound **3**: To a stirred solution of known compound **5** (2.00 g, 11.4 mmol) in DMF (10 mL) was added NIS (2.57 g, 12.6 mmol) at 0 °C. The reaction mixture was stirred at 22 °C for 1.5 h before it was diluted with EtOAc (80 mL). The resultant mixture was sequentially washed with saturated aq. $Na_2S_2O_3$ (20 mL) and brine (20 mL), and the organic phase was dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated under vacuum, and the crude iodide was dissolved in CH_2Cl_2 (10 mL). To this solution were sequentially added TsCl (2.61 g, 13.7 mmol), Et_3N (5.76 g, 7.93 mL, 57.0 mmol), and 4-DMAP (139 mg, 1.14 mmol) at 0 °C. The resultant mixture was allowed to warm to 22 °C and stirred at that temperature for 1 h before it was quenched with saturated aq. $NaHCO_3$ (30 mL). The mixture so obtained was extracted with EtOAc (3× 60 mL), and the combined organic phases were washed with brine (2× 20 mL) and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent under vacuum, the residue was subjected to flash column chromatography for purification using EtOAc/petroleum ether (1:5 → 1:1) as eluent to give α-iodoquinolone **3** (4.83 g, 93% for the two steps) as a yellow foam (Scheme 1). **3**: IR (film, cm^{-1}): ν_{max} 3063, 2929, 2843, 1593, 1560, 1483, 1263, 1180, 1037, 812, 870, 757, 677, 570; ^1H NMR (400 MHz, $CDCl_3$): δ 9.09 (s, 1H), 7.93 (d, 2H, J = 8.1 Hz), 7.57 (d, 1H, J = 8.6 Hz), 7.45 (t, 1H, J = 8.2 Hz), 7.40 (d, 2H, J = 8.1 Hz), 7.10 (d, 1H, J = 7.8 Hz), 4.08 (s, 3 H), 2.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.99, 155.09, 154.48, 146.16, 141.03, 133.49, 129.87, 128.65, 128.12, 126.01, 114.33, 108.70, 87.33, 56.08, 21.67; HRMS (m/z): $[M+H]^+$ calcd. for $C_{17}H_{15}O_4NIS^+$ 455.9761, found 455.9763.

The preparation of compound **7**: To a stirred solution of known β-hydroxy ketone **6** (2.00 g, 15.6 mmol) in DMF (1.0 mL) were sequentially added imidazole (5.31 g, 78.0 mmol) and TBDPSCl (21.4 g, 20.3 mL, 78.0 mmol) at 0 °C. The reaction mixture was allowed to warmed to 22 °C and stirred at that temperature for 1 h before it was quenched with saturated aq. $NaHCO_3$ (30 mL). The resultant mixture was extracted with EtOAc (3× 40 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and filtered. The solvent was evaporated under vacuum, and the residue was passed through a plug of silica with EtOAc/petroleum ether (1:20) to give the TBDPS ether as a colorless oil. This oil was dissolved in CH_2Cl_2 (15 mL). To this solution were sequentially added $NaHCO_3$ (1.70 g, 20.3 mmol) and m-CPBA (4.12 g, 20.3 mmol, 85 wt%) at 0 °C. The reaction mixture was allowed to warm to 22 °C and stir at that temperature for 5 h before it was quenched with saturated aq. Na_2SO_3 (50 mL). The resultant mixture was extracted with CH_2Cl_2 (3× 60 mL), and the combined organic phases were washed with brine (80 mL) and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent under vacuum, the residue was purified by flash column chromatography with EtOAc/petroleum ether (1:10 → 1:5) to give lactone **7** (5.19 g, 87% for the two steps) as a colorless oil (Scheme 1). **7**: IR (film, cm^{-1}): ν_{max} 3066, 2959, 2931, 2857, 1736, 1474, 1429, 1274, 1114, 1013, 819, 698; ^1H NMR (400 MHz, $CDCl_3$): δ 7.70–7.65 (m, 4H), 7.48–7.44 (m, 2H), 7.42–7.38 (m, 4H), 3.78 (dd, 1H, J = 6.0, 5.0 Hz), 2.61 (dd, 1H, J = 18.8, 7.4 Hz), 2.30 (dd, 1H, J = 18.8, 7.0 Hz), 1.81–1.76 (m, 2H), 1.42 (s, 3H), 1.31 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.29, 135.79, 135.71, 133.47, 132.60, 130.03, 129.96, 127.78, 127.68, 84.24, 71.35, 27.47, 26.95, 25.98, 24.31, 23.98, 19.37; HRMS (m/z): $[M+H]^+$ calcd. for $C_{23}H_{31}O_3Si^+$ 383.2037, found 383.2034.

The preparation of compound **4**: To a stirred solution of (trimethylsilyl)acetylene (6.00 g, 8.63 mL, 61.0 mmol) in THF



Scheme 1. Synthesis of the tetracyclic core of chlorospermines A and B. Reagents and conditions: (a) NIS (1.1 equiv.), DMF, 22 °C, 1.5 h; (b) TsCl (1.2 equiv.), Et_3N (5.0 equiv.), 4-DMAP (10 mol%), CH_2Cl_2, 22 °C, 1 h, 93% for the two steps; (c) TBDPSCl (5.0 equiv.), imidazole (5.0 equiv.), DMF, 22 °C, 1 h; (d) m-CPBA (1.3 equiv.), $NaHCO_3$ (1.3 equiv.), 22 °C, 5 h, 87% for the two steps; (e) TMS-acetylene (4.5 equiv.), BuLi (3.0 equiv.), $BF_3{\cdot}OEt_2$ (3.0 equiv.), THF, −78 °C, 2 h; (f) TFA (0.5 equiv.), 4 Å molecular sieves, CH_2Cl_2, 22 °C, 24 h; (g) K_2CO_3 (2.0 equiv.), MeOH, 22 °C, 2 h, 53% for the three steps; (h) $Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (5 mol%), Et_3N (5.0 equiv.), **3** (1.0 equiv.), DMF, 22 °C, 12 h, 75%; (i) Pt(dvds) (5 mol%), $(Et_2CHO)Me_2SiH$ (1.1 equiv.), CH_2Cl_2, 22 °C, 10 h; (j) AgF (3.0 equiv.), THF/MeOH/water (500:250:1), 22 °C, 3 h, 41% for the two steps; (k) air, toluene, 125 °C, 3 h, 56%.